Syntheses and Properties of Dithia-tetrahomodiaza-calix[4]arenes Bridged by Cystine Unit

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Dithia-tetrahomodiaza-calix[4]arenes were synthesized by the cyclization reactions of bis(3-(chloromethyl)-2-hydroxyphenyl)sulfide with cystine peptides in moderate yields. Conformational analysis of the macrocycles by using nmr spectroscopy reveled that the cyclophanes adopt a cone-like form as a preferable conformation and the cystine bridge moiety is incorporated in the cavity. The calixarene analogs can extract transion metals such as Zn^{2+} and Cu^{2+} ions from an aqueous phase into chloroform.

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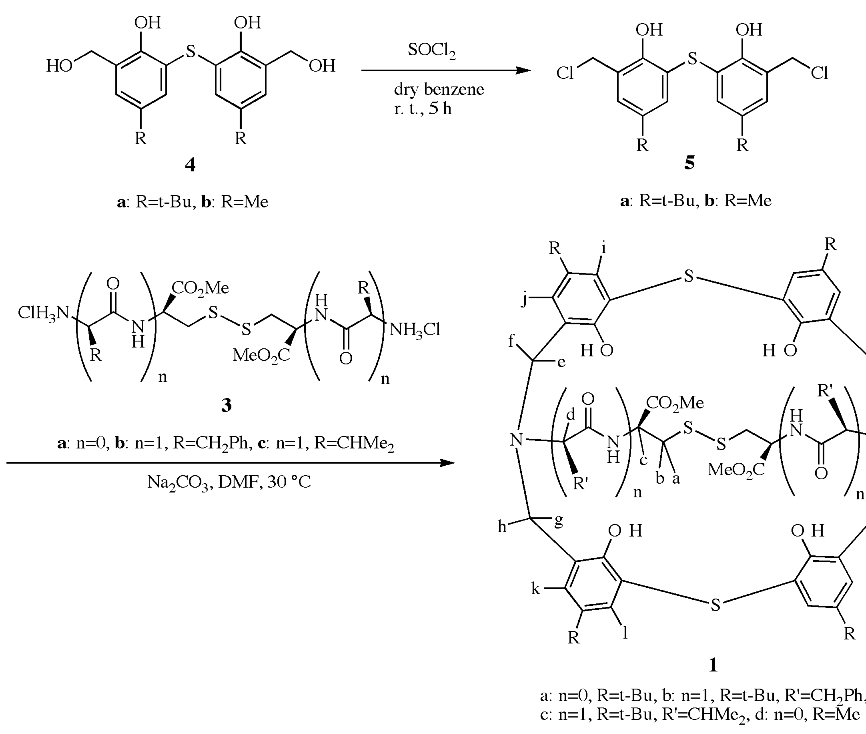
Introduction.

During the last two decades, the large number of published studies concerning calixarenes demonstrates a substantial interest in this class of molecules. Due to considerable synthetic effort, many calixarenes, in particular calixarene derivatives bearing a variety of functional groups at the small (lower) and/or large (upper) rims have been synthesized [1,2]. However, only recently a new class calixarene derivatives was reported in which the methylene bridges between the phenolic moieties was replaced by hetero atoms leading to heterocalixarenes [3-6]. These heteroatom bridges offer promising alternative to the original design of this class molecules leading to dramatic changes of their dynamic and complexation properties. In the present paper, we report the synthesis of dithia-tetrahomodiaza- calix[4]arenes in which four methylene bridges (-CH_2-) were replaced by two epithio groups (-S-) and two dihomoaza bridges (-CH_2NRCH_2-), their structural analysis and metal extraction ability.

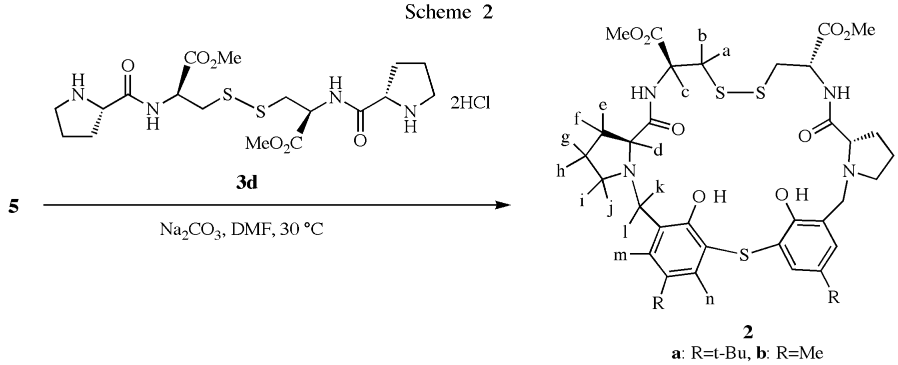
Results and Discussion.

Bis(3-(chloromethyl)-2-hydroxyphenyl)sulfide (**5**) were prepared by a chlorination of the corresponding bis(hydroxymethyl) compound (**4**) using thionyl chloride [7]. Cystine peptides (**3b-3d**) were synthesized by a solution phase synthetic method according to the literature. We carried out the cyclization reaction of **5a** with L-cystine dimethyl ester (**3a**) in the presence of sodium carbonate at room temperature in *N*,*N*-dimethyl formamide, and obtained dithia-tetra-

Scheme 1



Scheme 2



homodiaza-calix[4]arene (**1a**) bridged by cystine unit in 15 % yield (Scheme 1). Similarly, reactions of **5a** with cystine peptides (**3b** and **3c**) afforded the corresponding macrocycles (**1b** and **1c**) in 2 and 3 % yields, respectively [8]. Analogous reaction of **5b** with **3a** also gave **1d** in 20 % yield. When we used cystine peptide **3d** in the reaction with **5**, macrocycles (**2a** and **2b**) were afforded in 35 and 19 % yields, respectively (Scheme 2) [9].

The structures of the macrocycles (**1** and **2**) were established on the basis of their Fab-mass, nmr, and ir

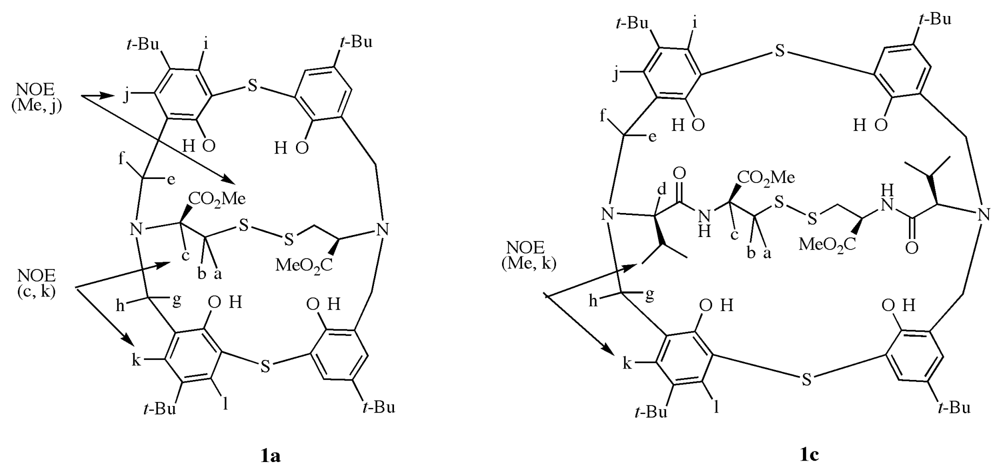


Figure 1. NOe Correlations.

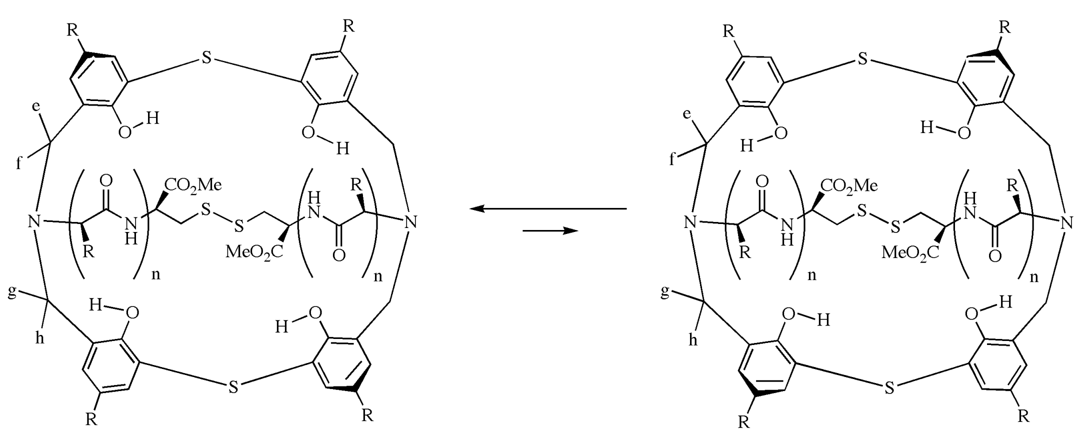


Figure 2. Schematic Representation of the Preferable Conformation of 1.

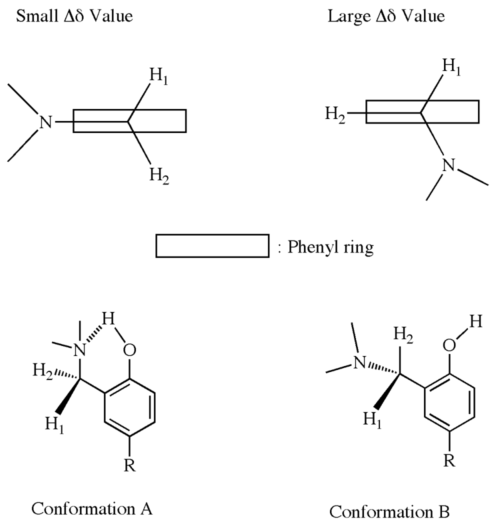


Figure 3. Conformational Dependence of Δδ Values between H_1 and H_2 Proton of the $ArCH_2N$ Methylene Moiety.

Table 1

Observed Proton Chemical Shifts and the Difference (Δδ) of the Checmial Shifts between Hexo and Hendo Proton of the NCH_2Ar Methylene Protons of **1a** and **1d** at Various Temperatures in Deuteriochloroform at 500 MHz

temperature	δH_e, δH_f (Δδ) [ppm]	δH_g, δH_h (Δδ) [ppm]	δ_{OH} [ppm]
	1a		
55 °C	3.67, 4.27 (0.60)	3.97, 4.18 (0.21)	9.00
40 °C	3.65, 4.27 (0.62)	3.99, 4.18 (0.19)	9.10
40 °C	3.64, 4.27 (0.63)	4.00, 4.18 (0.18)	9.20
0 °C	3.64, 4.27 (0.63)	4.02, 4.19 (0.17)	9.32
-20 °C	3.65, 4.28 (0.63)	4.07, 4.21 (0.14)	a
-40 °C	a	a	8.60, 10.75
-60 °C	a	a	8.50, 10.97
	1d		
55 °C	3.62, 4.20 (0.58)	4.01, 4.17 (0.16)	9.37, 9.59
40 °C	3.61, 4.20 (0.59)	4.02, 4.17 (0.15)	9.31, 9.71
20 °C	3.60, 4.21 (0.61)	4.04, 4.18 (0.14)	9.30, 9.78
0 °C	3.59, 4.22 (0.63)	4.06, 4.19 (0.13)	9.28, 9.86
-20 °C	3.57, 4.22 (0.65)	4.09, 4.20 (0.11)	9.00, 10.40
-40 °C	a	a	8.55, 10.80
-60 °C	a	a	8.50, 10.88

a: too broad to assign the signal

spectral data, and elemental anaylsis. The assignment of proton and carbon atoms was obtained by using 2D nmr experiments. In ^{1}H-nmr spectra of **1** in deuteriochloroform at 20 °C, the phenolic OH signals were observed in the range of δ 9.2-10.5 ppm [10]. Lowering the temperature to –60 °C slowed down the rate of proton exchange, and two signals with equal intensity appear (**1a**: δ 8.50, 10.97 ppm, **1b**: δ 9.25, 11.71 ppm, **1c**:δ 9.52, 12.00 ppm, **1d**: δ 8.50, 10.88 ppm). Considering that a nitrogen atom is a good proton acceptor, the OH peaks observed at lower magnetic field are assigned to the OH proton formed by hydrogen bonding not only with a hydroxyl group but also with the adjacent nitrogen atom [11]. In the ir spectra of **1** in chloroform, the OH stretching vibrations appeared in the range of 3330-3380 cm^{-1} as broad bands. These spectral data indicate the existence of intramolecular hydrogen bonding. The intramolecular hydrogen bonding in **1** is somewhat weaker than that of tetrahomodiazacalix[4]arene (δ_{OH} *ca.* 9 and 11-12 ppm, ν_{OH} 3270-3290 cm^{-1}) [12]. The ^{1}H- and ^{13}C-nmr spectra of **1** show a C_2 symmetry pattern. The Corey-Pauling-Koltum model consideration of **1** implied

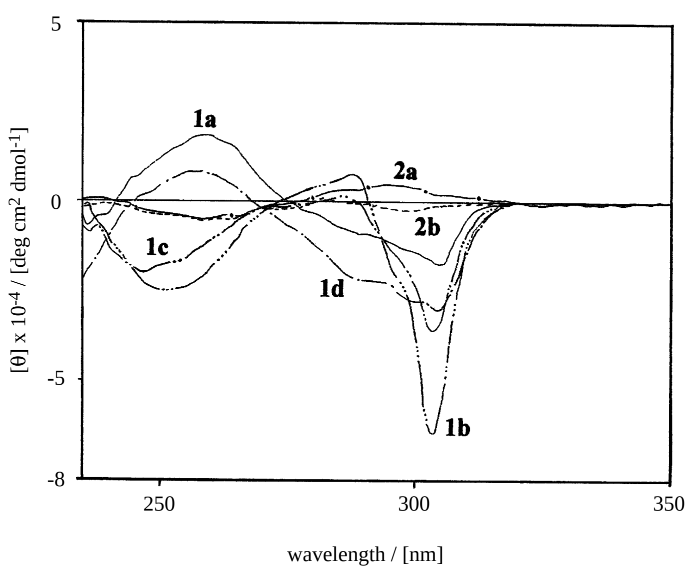


Figure 4. CD Spectra of **1** in chloroform at 20 °C

that it adopts a cone conformation because it is difficult to construct a 1,2-alternate model.

The nOe correlations observed for **1a** as shown in Figure 1 strongly suggest that the cystine bridge is located in the cavity of the cyclophane moiety. This is further supported by the fact that the chemical shift of H_a (δ 1.34 ppm) and H_b (δ 1.90 ppm) protons of **1a** were observed at higher magnetic field compared with analogous compound (**2a**) (H_a: 3.22 ppm, H_b: 3.32 ppm) due to shielding by the phenyl rings. Analogously, nOe cross peak were observed for **1c**, between methyl protons of the valine residue and aromatic proton H_k (Figure 1), implying that the cystine peptide bridge is also located in the cavity.

Since it is known that cyclophanes can bind quaternary ammonium ions, we used α-methylbenzyl trimethylammonium iodide as a guest, measuring the complexation by means of ^{1}H nmr spectroscopy in deuteriochloroform solution. However, the chemical shifts of the quaternary ammonium iodide scarcely changed in the presence of **1**. It may relate that the cystine bridge is located in the cavity.

Considering that the $\Delta\delta$ values of the $ArCH_2N$ methylene protons are expected to be sensitive to the dihedral angle between the methylene proton and the adjacent aromatic ring, the different between $\Delta\delta H_eH_f$ (0.63 ppm) and $\Delta\delta H_gH_h$ (0.18 ppm) for **1a** implies that sulfur-bridged phenol dimer moieties adopted a twisted form (Figure 2). Since the smaller $\Delta\delta$ values are ascribed to the CH_gH_h methylene protons, it is reasonable to assume that the methylene protons are located in an equivalent magnetic field (conformation A in Figure 3). In contrast, the larger $\Delta\delta$ values (CH_eH_f) indicate that the adjacent aromatic ring adopts a somewhat standup form (conformation B in Figure 3). A similar tendency was also observed in **1b** ($\Delta\delta H_eH_f$: 1.12 ppm and $\Delta\delta H_gH_h$: 0.90 ppm), **1c** ($\Delta\delta H_eH_f$: 1.24 ppm and $\Delta\delta H_gH_h$: 0.74 ppm), and **1d** ($\Delta\delta H_eH_f$: 0.61 ppm and $\Delta\delta H_gH_h$: 0.14 ppm). Based on these considerations, the sulfur-bridged phenol dimer moieties of **1** are considered to adopt a twisted structure as shown in Figure 2. The chirality of the L-cystine bridge prefers to form the left-hand isomer in Figure 2. In other words, the central chirality of the bridges transfers to the cyclophane moiety.

To prove the existence of chirality in the sulfur-bridged phenol dimer unit, we measured the circular dichroism spectra in chloroform at 20 °C. The circular dichroism spectra of **1** were clearly observed at *ca*. 300 nm (**1a**: 305 nm (θ -18900), **1b**: 304 nm (θ -66800), **1c**: 304 nm (θ-37300), **1d**: 307 nm (θ-29400)) due to the phenol chromophore, supporting the assumption that the dihydroxy diphenyl sulfide moieties assume a chiral conformation (Figure 4) [12]. In contrast, the circular dichroism spectral intensity of **2** was fairly small (**2a**: 298 nm (θ 6100), **2b**: 303 nm (θ-2800)). This indicates that the cystine bridge of **1** efficiently transfers chirality in this system.

In order to evaluate the temperature dependence of this chirality, we measured variable temperature ^{1}H nmr spectra of **1a** and **1d** in the range of 55 °C to –60 °C in deuteriochloroform. Lowering the temperature resulting in a decrease in the $\Delta\delta H_gH_h$ value and in an increase in the $\Delta\delta H_eH_f$ values (Table 1). The OH proton was observed as two kinds of peaks and shifted down field at low temperature. These results imply that cooling enhances the contribution of the twisted form.

We also studied the solvent extraction of various metals ions (Li^+, Na^+, K^+, Rb^+, Cs^+, Zn^{2+}, Cu^{2+}) by **1a** from an aqueous phase to a chloroform phase. Although **1a** could hardly extract alkali metal ions (percent extraction; Li^+ (5%), Na^+ (9 %), K^+ (2 %), Rb^+ (2 %), Cs^+ (2 %)), the transition metal ions (percent extraction; Zn^{2+} (61 %), Cu^{2+} (83 %)) were extracted effectively. Considering that calixarene can not extract any metal ions, these results can be rationalized by assuming that two epithio groups and dihomoaza bridges of **1a** can play an important role in the extraction of the transition metal ions [13,14].

In conclusion, we have demonstrated the first synthesis of chiral dithia-tetrahomodiaza-calix[4]arenes from the cyclization of bis(3-(chloromethyl)-2-hydroxyphenyl)-sulfide with cystine derivatives. Nmr and circular dichroism spectra of the macrocycles (**1**) show chiral transmission from the bridge to the cyclophane moiety. The macrocycle can extract transion metal ions such as Zn^{2+} and Cu^{2+} by solvent extraction method.

EXPERIMENTAL

Melting points were measured using a Yanagimoto Micro Melting Point Apparatus. ^{1}H and ^{13}C nmr spectra were measured with Varian Mercury 200 and Varian INOVA 500 spectrophotometers, using tetramethylsilane as an internal standard. Ir spectra were taken on a Horiba FT-200 spectrophotometer. Fab ms spectra were measured on JEOL AX-350 spectrometer, using *m*-nitrobenzyl alcohol as a matrix. Column chromatography on silica gel (Kieselgel 60, 63-200 mm, 70-230 mesh, Merck). All amino acid were used in the L-form. Cystine peptides (**3b**, **3c**, and **3d**) and bis(2-hydroxy-3-(hydroxymethyl)phenyl)sulfide (**4**) were prepared according to the methods reported in literature [7,8].

Synthesis of Bis(3-(chloromethyl)-2-hydoxyphenyl)sulfide (**5**).

To a solution of bis(2-hydroxy-3-(hydroxymethyl)phenyl)-sulfide (**4**) (7.6 mmol) in dry benzene (45 ml) was added a solution of thionyl chloride (5.5 ml, 76 mmol) in dry benzene (20 ml) at room temperature over 1 h. After the addition was complete, the mixture was stirred at room temperature for 4 h. Removal of benzene gave **5** as a colorless oil.

Compound **5a** was obtained as colorless oil. ^{1}H nmr (deuteriochloform): δ 1.23 (18H, s, *t*-Bu), 4.68 (4H, s, CH_2), 6.36 (2H, bs, OH), 7.29 (4H, s, Ar-H). ^{13}C nmr (deuteriochloroform): δ 31.1, 42.4, 119.1, 123.8, 128.6, 131.2, 144.5, 151.6. Fab-mass *m/z* 426 $(M+H)^+$.

Anal. Calcd. for $C_{22}H_{28}O_2Cl_2S_2$ C, 61.82; H, 6.60. Found C, 61.77; H, 6.55.

Compound **5b** was obtained as coloress oil. ^{1}H nmr (deuteriochloroform): δ 2.22 (6H, s, Me), 4.65 (4H, s, CH_2), 6.40 (bs, 2H, OH), 7.10 (2H, d, *J*=1.5 Hz, Ar-H), 7.12 (2H, d, *J*=1.5 Hz, Ar-H).

^{13}C nmr (deuteriochloroform): δ 20.4, 41.9, 119.2, 124.2, 131.0, 132.4, 134.7, 151.7. Fab-mass *m/z* 343 (M+H)$^+$.

Anal. Calcd. for $C_{16}H_{16}O_2Cl_2S_2$ C, 55.98; H, 4.70. Found C, 55.79; H,4.80.

General Procedure for the Preparation of Dithia-tetrahomodiaza-calix[4]arenes (**1**).

To a suspension of sodium carbonate (159 mg, 1.5 mmol) in dry *N*,*N*-dimethyl formamide (10 ml) were added a solution of **3** (0.25 mmol) in dry *N*,*N*-dimethyl formamide (10 ml) and a solution of **5** (214 mg, 0.5 mmol) in dry *N*,*N*-dimethyl formamide (10 ml) simultaneously at 30 °C over 0.5 h. After the addition was completed, the mixture was stirred at 30 °C for 10 h. Removal of *N*,*N*-dimethyl formamide under a reduced pressure below 40 °C gave pale yellow oily residue, which was subjected to column chromatography on silica gel using hexane:ethyl acetate 4:1 as an eluent to give **1** as crystals.

Compound **1a** was obtained in 15 % yield mp 140-145 °C. ^1H nmr (deuteriochloroform): δ 1.15 (18H, s, *t*-Bu), 1.24 (18H, s, *t*-Bu), 1.34 (2H, dd, *J*=10.5, 14.0 Hz, H_a), 1.90 (2H, dd, *J*=2.0, 14.0 Hz, H_b), 3.57 (2H, d, *J*=13.5 Hz, H_e), 3.74 (6H, s, CO_2CH_3), 3.87 (2H, dd, *J*=2.0, 10.5 Hz, H_c), 3.92 (2H, d, *J*=13.0 Hz, H_g), 4.10 (2H, d, *J*=13.0 Hz, H_h), 4.19 (2H, d, *J*=13.5 Hz, H_f), 6.91 (2H, d, *J*=2.5 Hz, H_j), 7.05 (2H, d, *J*=2.5 Hz, H_k), 7.43 (2H, d, *J*=2.5 Hz, H_l), 7.65 (2H, d, *J*=2.5 Hz, H_i), 9.20 (4H, bs, OH). ^{13}C nmr (deuteriochloroform): δ 31.4, 31.5, 34.0, 41.8, 51.6, 56.4, 59.4, 59.9, 120.8, 121.0, 121.6, 122.5, 128.8, 129.4, 132.2, 133.3, 142.8, 143.0, 154.2, 155.1, 169.9. Ir (chloroform) cm^{-1}: 3380 (ν_{OH}), 1734 (ν_{CO}). Fab-mass *m/z*: 978 (M+H)$^+$.

Anal. Calcd. for $C_{52}H_{68}N_2O_8S_4$: C, 63.90; H, 7.01; N, 2.87. Found: C, 64.10; H, 6.89; N, 2.91.

Compound **1b** was obtained in 2 % yield mp 190-193 °C. ^1H nmr (deuteriochloroform): δ 1.27 (18H, s, *t*-Bu), 1.33 (18H, s, *t*-Bu), 2.69 (2H, dd, *J*=1.5, 11.5 Hz, CH*H*Ph), 2.95 (2H, dd, *J*=9.5, 14.5 Hz, H_a), 3.25 (2H, dd, *J*=11.0, 11.5 Hz, C*H*HPh), 3.28 (2H, dd, *J*=4.0, 14.5 Hz, H_b), 3.33 (2H, dd, *J*=1.5, 11.0 Hz, H_d), 3.40 (2H, d, *J*=13.0 Hz, H_h), 3.54 (2H, d, *J*=14.5 Hz, H_f), 3.60 (6H, s, CO_2CH_3), 4.29 (2H, d, *J*=13.0 Hz, H_g), 4.64 (2H, ddd, *J*=4.0, 5.0, 9.0 Hz, H_c), 4.66 (2H, d, *J*=14.5 Hz, H_e), 6.83-6.87 (6H, m, Ph-H), 7.20 (2H, d, *J*=2.0 Hz, H_k), 7.63 (2H, d, *J*=2.0 Hz, H_i), 7.81 (2H, d, *J*=2.0 Hz, H_l), 10.50 (4H, bs, OH). ^{13}C nmr (deuteriochloroform): δ 27.5, 31.4, 31.5, 34.0, 34.1, 39.5, 52.4, 52.7, 55.0, 56.6, 63.0, 119.4, 121.0, 121.6, 121.8, 126.2, 127.8, 128.2, 129.4, 130.4, 133.3, 134.8, 137.9, 143.0, 154.4, 155.1, 170.5, 170.8. Ir (chloroform) cm^{-1}: 3330 (ν_{OH}), 1749 (ν_{CO}), 1684 (amide I), 1506 (amide II). Fab-mass *m/z*: 1272 (M+H)$^+$.

Anal. Calcd. for $C_{70}H_{86}N_4O_{10}S_4$: C, 66.11; H, 6.82; N, 4.41. Found: C, 65.98; H, 6.91; N, 4.22.

Compound **1c** was obtained in 3 % yield mp 130-132 °C. ^1H nmr (deuteriochloform): δ 0.74 (6H, d, *J*=7.0 Hz, CH_3), 1.06 (6H, d, *J*=7.0 Hz, CH_3), 1.25 (18H, s, *t*-Bu), 1.27 (18H, s, *t*-Bu), 2.50 (2H, m, $CH(CH_3)_2$), 2.77 (2H, d, *J*=10.0 Hz, H_d), 2.81 (2H, dd, *J*=12.0, 14.0 Hz, H_a), 3.31 (2H, dd, *J*=3.5, 14.0 Hz, H_b), 3.50 (2H, d, *J*=12.0 Hz, H_g), 3.71 (2H, d, *J*=14.5 Hz, H_e), 3.76 (6H, s, CO_2CH_3), 4.24 (2H, d, *J*=12.0 Hz, H_h), 4.70 (2H, ddd, *J*=3.5, 3.5, 12.0 Hz, H_c), 4.95 (2H, d, *J*=14.5 Hz, H_f), 6.93 (2H, bs, NH), 7.02 (2H, d, *J*=2.0 Hz, H_j), 7.06 (2H, d, *J*=2.0 Hz, H_k), 7.61 (2H, d, *J*=2.0 Hz, H_i), 7.77 (2H, d, *J*=2.0 Hz, H_l), 10.51 (4H, bs, OH). ^{13}C nmr (deuteriochloform): δ 20.6, 20.9, 27.2, 31.3, 31.4, 34.0, 36.8, 52.2, 52.5, 54.1, 57.7, 64.3, 119.5, 121.4, 121.6, 121.9, 127.5, 131.9, 132.9, 134.1, 142.8, 143.1, 154.4, 155.1, 171.5, 172.4. Ir (chloroform) cm^{-1}: 3330 (ν_{OH}), 1749 (ν_{CO}), 1684 (amide I), 1506 (amide II). Fab-mass *m/z*: 1176 (M+H)$^+$.

Anal. Calcd. for $C_{62}H_{86}N_4O_{10}S_4$: C, 63.34; H, 7.37; N, 4.77. Found: C, 63.55; H, 7.21; N, 4.55.

Compound **1d** was obtained in 20 % yield mp 253-255 °C. ^1H nmr (deuteriochloform): δ 1.74 (2H, dd, *J*=9.0, 12.5 Hz, H_a), 2.24 (12H, s, CH_3), 2.26 (2H, d, *J*=12.5 Hz, H_b), 3.60 (2H, d, *J*=12.5 Hz, H_e), 3.81 (12H, s, CH_3), 3.88 (2H, d, *J*=9.0 Hz, H_c), 4.04 (2H, d, *J*=13.0 Hz, H_g), 4.18 (2H, d, *J*=14.5 Hz, H_h), 4.21 (2H, d, *J*=13.5 Hz, H_f), 6.80 (2H, s, H_j), 6.90 (2H, s, H_k), 7.37 (2H, s, H_l), 7.44 (2H, s, H_i), 9.30 (2H, bs, OH), 9.78 (2H, bs, OH). ^{13}C nmr (deuteriochloform): δ 20.2, 32.1, 51.7, 60.3, 60.4, 120.7, 120.9, 122.0, 122.9, 129.1, 129.5, 132.6, 136.2, 136.8, 155.1, 170.1. Ir (chloroform) cm^{-1}: 3380 (ν_{OH}), 1732 (ν_{CO}). Fab-mass *m/z*: 786 (M+H)$^+$.

Anal. Calcd. for $C_{38}H_{44}N_2O_8S_4$: C, 58.14; H, 5.65. Found: C, 58.20; H, 5.42.

General Procedure for the Preparation of Macrocycles (**2**).

To a suspension of sodium carbonate (159 mg, 1.5 mmol) in dry *N*,*N*-dimethyl formamide (10 ml) were added a solution of **5** (0.5 mmol) in dry *N*,*N*-dimethyl formamide (10 ml) and a solution of **3d** (268 mg, 0.5 mmol) in dry *N*,*N*-dimethyl formamide (10 ml) simultaneously at 30 °C over 1 h. After the addition was completed, the mixture was stirred at 30 °C for 10 h. Removal of *N*,*N*-dimethyl formamide under a reduced pressure below 40 °C gave pale yellow oily residue, which was subjected to column chromatography on silica gel using ethyl acetate as an eluent to give **2** as crystals.

Compound **2a** was obtained in 35 % yield mp 146-148 °C. ^1H nmr (deuteriochloform): δ 1.28 (18H, s, *t*-Bu), 1.78 (4H, m, H_g and H_h), 1.97 (2H, m, H_f), 2.25 (2H, m, H_e), 2.33 (2H, m, H_j), 2.94 (2H, m, H_i), 3.19 (2H, m, H_d), 3.22 (2H, dd, *J*=5.0, 13.5 Hz, H_a), 3.32 (2H, dd, *J*=6.5, 13.5 Hz, H_b), 3.35 (2H, bs, H_k), 3.73 (6H, s, CO_2CH_3), 4.33 (2H, d, *J*=13.5 Hz, H_l), 4.83 (2H, ddd, *J*=5.0, 6.5, 6.5 Hz, H_c), 7.04 (2H, bs, H_m), 7.40 (2H, bs, H_n), 7.92 (2H, d, *J*=6.5 Hz, NH). ^{13}C nmr (deuteriochloform): δ 23.3, 30.1, 31.4, 39.6, 51.6, 52.7, 53.7, 67.7, 119.8, 123.2, 127.8, 131.1, 142.9, 153.4, 170.8, 174.0. Ir (chloroform) cm^{-1}: 3395 (ν_{OH}), 1745 (ν_{CO}), 1668 (amide I), 1508 (amide II). Fab-mass *m/z*: 817 (M+H)$^+$.

Anal. Calcd. for $C_{40}H_{56}N_4O_8S_3$: C, 58.80; H, 6.91. Found C, 58.90; H, 6.70.

Compound **2b** was obtained in 19 % yield mp 128-132 °C. ^1H nmr (deuteriochloform): δ 1.79 (4H, m, H_g and H_h), 1.99 (2H, m, H_f), 2.22 (6H, s, 6H), 2.25 (2H, m, H_e), 2.33 (2H, m, H_j), 2.93 (2H, m, H_i), 3.19 (2H, m, H_d), 3.23 (2H, dd, *J*=5.0, 14.0 Hz, H_a), 3.31 (2H, bs, H_k), 3.33 (2H, dd, *J*=6.5, 14.0 Hz, H_b), 3.73 (6H, s, CO_2CH_3), 4.29 (2H, d, *J*=13.5 Hz, H_l), 4.81 (2H, ddd, *J*=5.0, 6.5, 6.5 Hz, H_c), 6.86 (2H, bs, H_m), 7.22 (2H, bs, H_n), 7.94 (2H, bs, NH). ^{13}C nmr (deuteriochloform): δ 20.3, 23.3, 30.0, 39.8, 51.7, 52.7, 53.6, 57.3, 67.6, 120.1, 123.7, 129.3, 131.7, 134.7, 153.7, 170.8, 174.0. Ir (chloroform) cm^{-1}: 3396 (ν_{OH}), 1747 (ν_{CO}), 1670 (amide I), 1508 (amide II). Fab-mass *m/z*: 733 (M+H)$^+$.

Anal. Calcd. for $C_{34}H_{44}N_4O_8S_3$: C, 55.72; H, 6.05. Found C, 55.65; H, 5.99.

Solent Extraction.

To a 30 ml vial tube were pipetted a solution of **1a** (5 x 10^{-4} *M*) in chloroform (10 ml) and aqueous solution (10 ml) containing a metal ion (1 x 10^{-4} *M*), pH buffer (5 x 10^{-2} *M* Tris-HCl at pH 8.0). The mixture was shaken for 30 min. The total concentration of metal species remaining in aqueous phase was measured by Zeeman atomic absorption spectrometer.

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[9] Reactions of **5** with benzyl amine and L-amino acid methyl ester instead of cystine derivatives under several reaction conditions did not give any product except polymeric materials.

[10] The phenolic OH protons of **2** in the ^{1}H NMR spectra are too broad to observe the signal even at –60 °C in deuteriochloroform.

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